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(54) Title: A MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ANTIGEN IN A VACCINE AGAINST AN IMMUNODEFICIENCY VIRUS

(57) Abstract

A major histocompatibility complex class II antigen is useful as a vaccine against an immunodeficiency virus. The antigen may be a human class II antigen such as HLA-DP, HLA-DQ or HLA-DR. The virus may be a human immunodeficiency virus (HIV) such as HIV-1 or HIV-2.

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A MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ANTIGEN IN A VACCINE AGAINST AN IMMUNODEFICIENCY VIRUS

This invention relates to vaccines against immunodeficiency viruses.

There has been pessimism about the prospects for a successful vaccine against AIDS. The obstacles have often appeared to be insuperable. An effective vaccine must prevent infection by a virus which destroys $CD4^+$ cells, which can integrate into the host DNA and which exhibits rapid antigenic variation. Furthermore, protection must be effective at mucosal surfaces, the primary site of entry, and against both cell-free and cell-associated virus. The simian immunodeficiency virus (SIV)-macaque model, developed in the USA[1,2], was adopted by the United Kingdom MRC AIDS Directed Programme with the primary objective of establishing that vaccination was feasible and that these obstacles to success could be overcome.

We have now demonstrated that a major histocompatibility complex (MHC) class II antigen can protect animals in the SIV-macaque model. Accordingly, the invention provides a class II antigen for use in a method of treatment of the human or animal body by therapy, in particular for use as a vaccine against an immunodeficiency virus.

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a MHC class II antigen. The invention further provides use of a MHC class II antigen in the manufacture of a medicament for use as a vaccine against an immunodeficiency virus.

The antigen is preferably a human class II antigen. The antigen may therefore be a HLA-DP, HLA-DQ or HLA-DR antigen such as the HLA-DR4 antigen. These are known antigens and can be obtained in purified form. They may be prepared as recombinant proteins.

Alternatively, the class II antigen may be given presented by transfected cells, i.e. by cells transfected with a gene encoding the antigen and which consequently express the antigen. Transfected cells which may be administered to a human may be transfected cells of a human diploid cell line. Such cell lines have been tested for safety for the purpose of

human vaccine manufacture. An appropriate cell line is the MRC5 cell line.

Allogeneic lymphocytes which present a class II antigen may be administered to a patient. The lymphocytes may be given as live cells, for example as a blood transfusion. Alternatively they may also be given as fixed or inactivated cells. The lymphocytes may be ones in which the expression of the class II antigen has been enhanced, for example by stimulation with a mitogen or gamma-interferon.

The antigen may be used to vaccinate a host against an immunodeficiency virus. The host may be a human or animal but typically it will be wished to vaccinate a human against a human immunodeficiency virus (HIV). That virus may be HIV-1 or HIV-2. A prophylactic treatment for disease states attributable to infection by an immunodeficiency virus can therefore be provided. The class II antigen may in particular act as an AIDS vaccine.

An effective amount of the antigen is administered to a host it is wished to vaccinate. The antigen in whichever form, can be given parenterally, for example subcutaneously, intramuscularly or intravenously. The amount of antigen per dose depends on a variety of factors such as the age and the condition of the subject involved. A parenteral dose typically consists of from 20μg to 1 mg of antigen, for example from 50 to 500 μg of antigen. A number of doses may be given, for example from 2 to 4 doses over a period of up to six months. Each dose may be given one or two months apart.

An agent for use as a vaccine against an immunodeficiency virus is therefore provided. A pharmaceutical composition also comprising a pharmaceutically acceptable carrier or diluent can be formulated. The composition is thus sterile and pyrogen-free. The composition may also comprise an adjuvant such as $Al(OH)_3$ or saponin.

Compositions for intramuscular or subcutaneous injections may contain together with the antigen a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain

as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The MHC class II antigens can be safely used by virtue of their negligible toxicity.

The following Examples illustrate the invention.

Example 1

Inactivated Vaccines

In initial experiments relatively crude, inactivated vaccines were deliberately used (Table 1). The virus infected C8166 cells (Virology, 129, 51-64, 1983 in which the cells are called C63/CR11-2 cells) or partially purified virus, inactivated either by aldehydes or β-propiolactone, were given to groups of three or four cynomolgus macaques. Four doses of vaccine were administered with a rest period of at least six months between the third and final doses. Three different adjuvants were used, either Quil-a (a purified saponin), SAF-1 (Syntex emulsion containing threonyl muramyl di-peptide) or Freund's adjuvant. Each group of vaccinated animals, together with a group of unvaccinated controls, was challenged intravenously with $10MID_{50}$ of the 32H isolate of SIVmac251, two weeks after the final dose of vaccine. All control animals became infected. Virus was repeatedly isolated and proviral DNA detected in peripheral blood lymphocytes after amplification by polymerase chain reaction. Furthermore significant antibody responses to SIV were detected. In contrast there was no evidence of virus infection to any of the vaccinated animals by any of these criteria. These experiments with inactivated virus vaccines have been extended to show that the immunization schedule can be reduced to three doses given at monthly intervals. The duration of protection was assessed by re-challenging animals four to six months after the final dose of vaccine. Five of eight macaques were protected. These results together with other published data[2,3,4,5] demonstrate that inactivated vaccines induce a powerful protection against SIV infection in macaques and that this protection is still detectable at least 6 months after the completion of vaccination.

Cross-Protection

The breadth of protection induced by SIV vaccines

was investigated by vaccinating eight rhesus and eight cynomolgus macaques with formalin inactivated SIV using SAF-1 as adjuvant. Two weeks after the fourth dose of vaccine, four rhesus and four cynomolgus monkeys were challenged with the homologous virus. All eight animals were completely protected against infection. The four remaining rhesus monkeys were challenged with $10MID_{50}$ of $SIV_{deltaB670}$ (kindly supplied by Dr. M. Murphy-Corb). These animals also resisted infection. The remaining four cynomolgus macaques were challenged with $10MID_{50}$ of $HIV\text{-}2_{SBL6669}$ (kindly supplied by Drs. P. Putkonen and G. Biberfield). These animals all became infected. Analysis of the viruses involved in these cross-protection experiments revealed that SIVmac251 and SIV_{delta} share 83% identity in the amino acid sequences of their envelope proteins. In contrast, SIVmac251 and $HIV\text{-}2_{SBL}$ are only 73% identical in the envelope protein. The antigenic diversity of these viruses was established using a panel of 30 monoclonal antibodies made against the envelope protein of SIVmac251. Although all of these antibodies reacted with the vaccine virus in an ELISA assay, 11 failed to react with SIV_{delta} and 20 failed to reach with $HIV\text{-}2_{SBL}$. These results indicate that inactivated vaccine prepared from SIVmac completely protects animals against challenge with the antigenically distinct strain of SIV_{delta}, but that this cross-protection does not extend to the more distantly related HIV-2 virus. Thus, the antigenic variability of immunodeficiency viruses may not be as big an obstacle to successful vaccination as was originally feared. However, this conclusion may require reinterpretation in the light of anti-cell responses discussed below.

Mucosal Immunity

The problem of inducing protection at a mucosal surface was investigated using the intrarectal route of challenge. The standard challenge virus pool of the 32H isolate of SIVmac251, which had been used in all the previous intravenous challenges, was first titrated in rhesus macaques using the intrarectal route. One thousand times more viruses was required to infect monkeys by this route, but the subsequent course of infection was essentially indistinguishable from that following intravenous inoculation.

Four rhesus macaques were then vaccinated subcutaneously with formalin-inactivated SIV using SAF-1 as adjuvant. Two weeks after the fifth dose of vaccine the animals were challenged intrarectally with $10MID_{50}$ based on the intrarectal titration. Four unvaccinated control animals challenged at the same time all became infected. In contrast, all four of the vaccinated animals have remained uninfected over a period of at least six months. This experiment indicates that immunity can be induced against challenge via a mucosal surface.

Challenge with Cell-Associated Virus

A cell associated challenge virus stock was prepared from the spleen of a cynomolgus macaque J82 which had been infected with the 32H isolate of SIVmac251 ten weeks previously. Aliquots of the cells were cryopreserved and then titrated in vitro by co-cultivation with C8166 cells (Table 2). The infectivity titres of the cells and their supernatant fluid were $\log_{10}$ 4.5 and 2.5 respectively. Thus 99% of the infectivity was cell-associated and one ID_{50} was equivalent to 72 viable cells. Subsequent titration of the spleen cells in vivo in monkeys gave an end-point of $\log_{10}$ 3.0 with one ID_{50} being equivalent to 2,300 cells. Having prepared and titrated intravenously an appropriate cell-associated virus challenge, four cynomolus macaques were selected which had previously been vaccinated subcutaneously with inactivated SIV and shown to be protected against intravenous cell-free virus challenge. These animals which had remained free of virus for twelve months following initial challenge were revaccinated and two weeks later challenged intravenously with cell-associated virus (Table 3). The four vaccinated animals, together with four unvaccinated controls, all became infected. Virus and proviral DNA were detected repeatedly in the peripheral blood lymphocytes. Thus a vaccine which had protected against intravenous challenge with cell-free virus grown in a human T-cell line failed to protect against SIV infected simian spleen cells.

Recombinant Vaccines

The specific compounds within the inactivated vaccine which were responsible for the protection were next sought by immunization with a variety of recombinant proteins

derived from SIV genes. Groups of four monkeys were immunised either with p27 expressed on yeast virus-like particles and combined with aluminium hydroxide, or with purified gp160 derived from a recombinant vaccinia virus, or gp130 expressed in CHO cells, or gp140 expressed by baculovirus. Each of the envelope proteins was administered with the Syntex adjuvant formulation. Vaccines were given in four doses and the animals were challenged with $10MID_{50}$ of SIV two weeks after the final dose, together with groups of four unvaccinated control animals. All of these monkeys became infected except one which was vaccinated with the baculovirus derived gp140. Thus although recombinant proteins were able to induce high titres of antibody against SIV envelope, they were not able to protect animals against intravenous challenge.

Immune Correlates of Protection

The immune responses which correlated with protection were analysed by measuring antibody titres in sera taken on the day of challenge from 55 vaccinated macaques used in these studies. Forty three animals had received inactivated vaccines and 12 a recombinant envelope protein (Table 4). Neutralising antibodies were measured against SIVmac251 grown as a persistent infection in HUT-78 cells. The mean titre of neutralizing antibody in the group of 32 macaques which received inactivated vaccine and were protected was $\log_{10}$ 2.0 $\pm$ 0.5. The same mean value was found in the group of 11 animals which were unprotected. Furthermore the 11 animals vaccinated with recombinant envelope proteins and unprotected, had a higher mean titre of $\log_{10}$ 2.9 $\pm$ 0.5. Thus there was no clear correlation between titres of neutralising antibodies and protection in these animals. Titration of these sera against recombinant envelope gp140 by ELISA also failed to show any correlation with protection. Similarly, although these vaccines induced strong T-helper cell proliferation responses to SIV, and in some cases MHC class-II restricted cytotoxic cells, there was no obvious correlation between the cellular responses to SIV and protection. Our failure to find any correlation between the powerful protection we have observed following vaccination and any of the immune responses which we had measured was disturbing. However, it is possible that the

immunological assays we used were inappropriate.

Responses to Cell Components

At this point results of a further vaccine experiment began to emerge which offered explanation for our observations (Table 5). This experiment was originally designed to examine if the two doses of vaccine were sufficient to protect against intravenous challenge with cell-fee virus. Four cynomolgus macaques were vaccinated with SIV-infected C8166 cells using Quil-A as adjuvant at weeks 0 and 4. A control group of four animals were similarly vaccinated but with uninfected C8166 cells. Both groups were challenged with $10MID_{50}$ of virus two weeks after the second dose of vaccine. One of the four animals vaccinated with SIV-infected cells became infected but, surprisingly, only two of the four vaccinated with uninfected cells became infected. In order to confirm these surprising results the protected animals were further vaccinated at week 26 and re-challenged two weeks later together with four naive control macaques. Partial protection was again observed in the animals immunised with uninfected C8166 cells, whereas all four unvaccinated control animals became infected. Antibodies to the cellular component of these vaccines were measured by ELISA using a detergent lysate of C8166 cells as antigen (Table 6). The mean titre of antibody in the eight protected animals was $\log_{10}$ 3.5 and in the five unprotected animals $\log_{10}$ 2.4. The difference between these two groups was highly significant. Analysis of anti-cell antibody levels in all the animals which had received inactivated vaccines showed a similar difference between protected and unprotected animals. Thus there was a statistical correlation between the titre of antibody to C8166 cells and protection in these animals.

Conclusions

These studies demonstrate that at least 3 different inactivated vaccines protect against homologous cell-free SIV. The protection induced is potent since neither virus nor proviral DNA can be detected in the vaccinated animals over prolonged periods following challenge. Five different adjuvants and a variety of immunization procedures are effective. The inactivated vaccines protect against

heterologous challenge with SIV_{delta} but not against HIV-2. The immunity against challenge is reduced but still detectable at four and eight months post-vaccination. Parenteral vaccination with inactivated virus protects against intrarectal challenge with cell-free virus, but not against intravenous challenge with SIV-infected simian spleen cells. Three different preparations of SIV envelope protein were shown to be highly immunogenic, but failed to protect against live intravenous challenge. The protection observed failed to correlate with any of the immune reactions to SIV which were measured. However there was a correlation between protection and levels of antibody to C8166 cells. These results suggest that the protection observed may be mediated at least in part, by immune responses to cellular components present within the inactivated vaccines.

TABLE 1 SUCCESSFUL INACTIVATED SIV VACCINES

VACCINATION		DOSES (WEEKS)	OUTCOME OF CHALLENGE*	
ANTIGEN	ADJUVANT		CONTROLS	VACCINATES
GLUTARALDEHYDE FIXED SIV-INFECTED CELLS (32H)	QUIL-A	0, 4, 8, 36	4/4	0/4
FORMALDEHYDE FIXED SIV (32H)	SAF-1	0, 4, 8, 32	4/4	0/4
B-PROPIOLACTONE INACTIVATED SIV (BK28)	FREUNDS	0, 4, 8, 39	4/4	0/3

ANIMALS WERE CHALLENGED INTRAVENOUSLY 2 WEEKS AFTER VACCINATION WITH 10 MID_{50}.

* NUMBER INFECTED/NUMBER CHALLENGED

TABLE 2 TITRATION OF CELL ASSOCIATED VIRUS

DILUTION	VIABLE CELLS	INFECTIVITY (NO.INFECT/NO.INOC)		
		CELL CULTURE		MACAQUES
		SUPER	CELLS*	CELLS*
-2	$2.3x10^4$	4/4	4/4	4/4
-3	$2.3x10^3$	0/4	4/4	1/2
-4	$2.3x10^2$	0/4	4/4	0/2
-2	$2.3x10^1$	0/4	0/4	0/2
LOG ID_{50}	-	2.5	4.5	3.0
CELL/ID_{50}	-	-	72	2300

* SPLEEN CELLS FROM SIV-INFECTED CYNO J82

TABLE 3 CHALLENGE WITH CELL-ASSOCIATED SIV

VACCINE	DOSES (WEEKS)	OUTCOME+ NO. INFECT/NO. CHALL
500µG FORMALDEHYDE INACTIVATED SIV + MDP	0, 4, 8, 32 (34)* 83	4/4
GLUTARALDEHYDE INACTIVATED CELLS INFECTED WITH VACC-ENV+GAG + QUIL A	0, 4, 8, 18, 22 41, (43)*, 54	4/4
NONE	-	4/4

* DATE OF INTRAVENOUS CHALLENGE WITH CELL-FREE VIRUS.

\+ ALL ANIMALS CHALLENGED INTRAVENOUSLY WITH INFECTED SPLEEN CELLS TWO WEEKS AFTER LAST DOSE OF VACCINE.

TABLE 4 NEUTRALIZING ANTIBODIES AND PROTECTION

VACCINE	OUTCOME OF CHALLENGE	NO. ANIMALS	ANTIBODY TITRE*	
			MEAN	SD
INACTIVATED	PROTECTED	32	2.0	0.5
	UNPROTECTED	11	2.0	0.4
RECOMBINANT	PROTECTED	1	(3.1)	-
	UNPROTECTED	11	2.9	0.5

* TITRE EXPRESSED AS LOG_{10}

TABLE 5 VACCINATION WITH C8166 CELLS (TRIAL 22)

VACCINE	DOSES (WEEKS)	CHALLENGE	
		WEEK	OUTCOME*
SIV-INFECTED C8166 CELLS + QUIL A	0, 4 26	6 28	1/4 1/3
UNINFECTED C8166 CELLS + QUIL A	0, 4 26	6 28	2/4 1/2
NONE	-	-	4/4

* NO INFECT/NO CHALLENGED

TABLE 6 CORRELATION OF PROTECTION WITH ANTIBODY TO C8166 CELLS

POPULATION	STATUS	NO.	ANTIBODY TITRE*			P.
			MEAN	±	SD	
TRIAL 22 (SEE TABLE 5)	PROTECTED	8	3.5	±	0.18	<0.0001
	UNPROTECTED	5	2.4	±	0.20	
ALL ANIMALS GIVEN INACTIVATED VACCINES	PROTECTED	40	3.4		0.56	<0.0001
	UNPROTECTED	15	2.2		0.30	

* TITRES EXPRESSED AS LOG_{10}

Example 2

To confirm the protection influenced by uninfected human T cells, a second experiment was initiated (Table 6). Groups of 4 cynomolgus macaques were vaccinated with either C8166 cells (a human T cell line) or RK-13 cells (rabbit kidney fibroblasts). A third group acted as naive controls. The cells were gently fixed with 0.075% glutaraidehyde and combined with Quil A (a purified saponin) as adjuvant. Each dose comprised 2 x 10^8 cells and 10μg of Quil A. The vaccines were administered subcutaneously at 0, 4, 8 and 16 weeks. Two weeks after the final dose of vaccine all 12 macaques were challenged with 10 monkey infectious doses (MID_{50}) of simian immunodeficiency virus (SIVmac32H) which had been grown in C8166 cells. Virus and proviral DNA was detected in all the control animals and those vaccinated with RK-13 cells but in only two of the four given C8166 cells (Table 2.1).

To confirm and extend this observation the two protected animals were given another dose of C8166 cells at 30 weeks. Two weeks later they, and four naive controls, were challenged with 10 MID_{50} of an antigenically distinct virus, SIVsm3 which had been grown in human peripheral blood mononuclear cells (PBMC) from at least two donors. The controls were all infected but the two vaccinates remained protected.

Finally, the protected animals were vaccinated again at 44 weeks and challenged, together with four controls, with 10 MID_{50} of SIVmac251 grown in simian PBMC. All the animals became infected.

This experiment confirms that uninfected human T cells protect against at least two antigenically distinct strains of SIV grown in human T cells which need not be identical with the cells used as the vaccine. This protection did not extend to SIV grown in simian cells.

Table 6: Uninfected Cell Vaccines

VACCINE	DOSES (WKS)	OUTCOME OF CHALLENGE *		
		1st	2nd	3rd
Uninfected C8166 cells + Quil A	0,4,8,16 30 44	2/4	0/2	2/2
Uninfected RK-13 cells + Quil A	0,4,8,16	4/4	-	-
None	-	4/4		
None			4/4	
None				4/4

* No. monkeys infected/No. monkeys challenged

Example 3

The major antigens present on the surface of allogeneic or xenogeneic T cells are the major histocompatibility antigens (MHC) class I and class II. To determine if these were responsible for the protection observed groups of four cynomolgus macaques were immunised with either a) normal mouse fibroblasts (L cells), b) L cells (8024 line) transfected with the human genes for MHC class I (HLA B7 + β_2 microglobulin) or c) L cells (8115 line) transfected with the human genes for MHC class II (HLA-DR4). By fluorescent antibody staining, over 90% of 8024 and 8115 cells were expressing class I or class II antigen respectively. The cells were gently fixed in 0.075% glutaraldehyde and combined with 10μg of Quil A as adjuvant (Table 7). Animals were given 2 x 10^6 cells subcutaneously on four occasions at 0,4,8 and 16 weeks. Two weeks after the last dose, all twelve animals were challenged intravenously with 10 MID_{50} of SIVmac32H grown in C8166 cells. All the animals in groups a) and b) became infected but only two of four given cells expressing class II.

This result demonstrates that human MHC class II, namely HLA-DR4, can protect animals against SIV grown in human T cells.

Table 7: MHC Class I or Class II Vaccines

VACCINE	DOSES (WEEKS)	OUTCOME *
a) Normal L cells	0,4,8,16	4/4
b) L cells (8024) expressing class I	0,4,8,16	4/4
c) L cells (8115) expressing class II	0,4,8,16	2/4

* No. monkeys infected/No. monkeys challenged with SIVmac32H.

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CLAIMS

1. A major histocompatibility complex class II antigen for use in a method for treatment of the human or animal body by therapy.

2. An antigen according to claim 1 for use as a vaccine against an immunodeficiency virus.

3. An antigen according to claim 2, wherein the virus is human immunodeficiency virus (HIV).

4. An antigen according to claim 3, wherein the virus is HIV-1.

5. An antigen according to claim 3, wherein the virus is HIV-2.

6. An antigen according to any of the preceding claims, which is a human class II antigen.

7. An antigen according to claim 6, which is a HLA-DP, HLA-DQ or HLA-DR antigen.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a major histocompatibility complex class II antigen.

9. Use of a major histocompatibility complex class II antigen in the manufacture of a medicament for use as a vaccine against an immunodeficiency virus.

10. A method of vaccinating a host against an immunodeficiency virus, which method comprising administering to the host an effective amount of a major histocompatibility complex class II antigen.

11. An agent useful as a vaccine against an immunodeficiency virus, which agent comprises a major histocompatibility complex class II antigen.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00102

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K15/14; A61K39/385; A61K39/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 226 513 (INSTITUT PASTEUR) 24 June 1987 see the whole document ---	1-11
X	IMMUNOLOGY LETTERS vol. 24, no. 2, May 1990, AMSTERDAM, THE NETHERLANDS pages 127 - 131 D. LEWIS ET AL. 'HLA-DR peptide inhibits HIV-induced syncytia.' see abstract -----	1-11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08 APRIL 1993	27.04.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	NOOIJ F.J.M.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/GB93/00102

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of the human /animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300102
SA 68983

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 08/04/93

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		WO-A- 8703601	18-06-87
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